Med Genet 1999;**36**:565-566 (July)

short report

Fragile X syndrome with FMR1 and FMR2 deletion

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Received 29 July 1998; Revised version accepted for publication 5 February 1999

Abstract

We report a 13 year old boy with fragile X syndrome resulting from a de novo deletion of the FMR1 and FMR2 genes extending from (and including) DXS7536 proximally to FMR2 distally. The patient has severe developmental delay, epilepsy, and behavioural difficulties, including autistic features. He has epicanthic folds, in addition to facial features typical of fragile X syndrome, and marked joint hypermobility. We compare our patient to the three other cases reported in which both FMR1 and FMR2 are deleted. This case has the smallest deletion reported to date. All four patients have epilepsy and a more severe degree of mental retardation than is usual in fragile X syndrome resulting from FMR1 triplet repeat expansion. Three of the patients have joint laxity and two have epicanthic folds. We suggest that these features, in particular severe developmental delay and epilepsy, may form part of the characteristic phenotype resulting from deletion of both FMR1 and FMR2 genes. The diagnosis in this case was delayed because routine cytogenetics showed no abnormality and standard molecular tests for FMR1 triplet repeat expansion (PCR and Southern blotting) failed. Further DNA studies should be undertaken to investigate for a deletion where clinical suspicion of fragile X syndrome is strong and routine laboratory tests fail.
J Med Genet 1999;**36**:565-566)

Keywords: fragile X; FMR1; FMR2; deletion

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Fragile X syndrome is the commonest inherited cause of mental retardation, with a prevalence of between 1 in 4000 to 1 in 6000 males.[1 2] Most cases are the result of amplification of a CGG trinucleotide repeat sequence located in the 5' untranslated region of the FMR1 (FRAXA) gene on the long arm of the X chromosome. This sequence is unstable, a triplet repeat number of greater than approximately 200 causing inhibition of transcription of FMR1. Rarely, the clinical syndrome may result from deletion of all or part of the FMR1 (FRAXA) gene.[3] In three cases reported previously, the FMR2 (FRAXE) gene lying just distal to FMR1 was also deleted.[4-6] We describe a boy with a de novo deletion of the entire FMR1 and FMR2 genes and compare his features with those of the other reported cases.

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The patient was born after an uneventful pregnancy by elective caesarian section for breech presentation. His birth weight was 4692 g and there were no perinatal problems. There was no relevant family history. Severe developmental delay became evident in the first year of life. He sat at 10 months and walked at 2 years 10 months. Now aged 13 years, he can speak in short sentences and has behavioural difficulties, with aggression and agitation. He also has autistic features including a dislike of change in routine and hand flapping. Since 21/2 years he has had severe polymorphic epilepsy which has been difficult to control despite several anticonvulsant medications.

On examination, he has a large head (circumference above the 97th centile), a long face with prominent forehead and jaw, epicanthic folds, large ears, and marked joint hypermobility (fig 1). He also has a convergent squint.

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Figure 1 The proband. Note (A) prominent forehead and jaw and epicanthic folds, (B) prominent ears, and (C) marked joint laxity. (Photographs reproduced with permission.)

The karyotype was normal including culture in folate deficient medium. Routine molecular analysis by polymerase chain

eaction (PCR) and Southern blotting using techniques designed to assess the size of the FMR1 triplet repeat region failed o produce a result. Further molecular investigation of regions flanking the gene showed that this was because of a de novo leletion of the entire FMR1 and FMR2 genes extending from (and including) DXS7536 proximally to FMR2 distally (fig 2).

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Figure 2 Map of the X chromosome in the region Xq26.1-Xq28 showing the markers deleted in this patient. Other deletions in this region are shown for comparison. The figures beside the markers represent physical distances from F9 in megabases (Mb) as reported in the Genetic Location Database (GLD) (http://cedar.genetics.soton.ac.uk). DXS7536 and DXS8028 are shown in brackets because although the GLD suggests that DXS8028 is distal to DXS7536, in our patient DXS7536 was deleted while DXS8028 was not, implying that the order of markers is as shown.

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Table 1 compares our patient with the other cases reported in which both FMR1 and FMR2 are deleted. He has the smallest deletion reported to date.

Table 1 Comparison of clinical features in patients with deletion of FMR1 and FMR2

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Epilepsy is seen in all four patients with deletions of both FMR1 and FMR2, who also have more severe intellectual impairment and a greater degree of joint laxity than is usual in patients with fragile X syndrome owing to FMR1 triplet repeat expansion. Our patient has epicanthus which is also seen in the case of Tarleton *et al*[4] and Albright *et al*.[5]

In patients with deletion of FMR1 but intact FMR2, severe epilepsy and marked joint laxity are not common.[3] These patients often have typical facial features, and the occurrence of atypical features such as eunuchoid habitus, cherubism, prominent occiput with double hair whorl, shawl scrotum, and anal atresia may be the result of deletion of other adjoining genes.

The FMR2 associated phenotype is said to be milder than that caused by loss of expression of FMR1. However, losing both

FMR1 and FMR2 genes appears to cause a more severe disorder of brain development. The clinical features shared by our patient and those previously reported with FMR1 and FMR2 deletions, in particular moderate to severe developmental delay and epilepsy, suggest that these may be characteristic features which result from loss of both these genes. Further case reports will help to define this phenotype more clearly.

Finally, it should be noted that the diagnosis in our patient was delayed because routine laboratory investigations were negative (cytogenetics) or failed (DNA). Further investigations of DNA from the child and his mother indicated that the "failure" of the routine DNA test was the result of a de novo deletion in the child. It is important to be aware of this mechanism and to undertake further DNA studies if there is a strong clinical suspicion of fragile X syndrome.

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Mosaicism for FMR1 and FMR2 deletion: a new case
J. Med. Genet., March 1, 2002; 39(3): 200 - 201.
[Full Text]

Attachment 2

Journal Article

Observation of an excess of fragile-X premutations in a population of males referred with spinocerebellar ataxia

Journal	Human Genetics
Publisher	Springer Berlin / Heidelberg
ISSN	0340-6717 (Print) 1432-1203 (Online)
Subject	Biomedical and Life Sciences and Medicine
Issue	Volume 112, Numbers 5-6 / May, 2003
Category	Letter to the Editors
DOI	10.1007/s00439-003-0939-z
Pages	619-620
SpringerLink Date	Thursday, February 19, 2004

Authors

James Macpherson, Andrew Waghorn, Simon Hammans, Patricia Jacobs

Abstract

Premutations of the fragile-X (FRAXA) gene were thought to have no clinical effects until recent reports of an increased incidence of premature ovarian failure in females and a late-onset neurological disorder in males. These patients were identified from families including typical fragile-X males with a full mutation. By analysing a cohort of patients with neurodegenerative disorders referred for genetic analysis of spinocerebellar ataxia genes, we have found that 3 of 59 males carry the premutation. Our patients extend the phenotype associated with the FRAXA premutation and indicate that it may account for a proportion of undiagnosed neurodegenerative disorders.

Attachment 3

The Drosophila Model of Fragile X Syndrome: Testing the Metabotropic Glutamate Receptor Hypothesis

Kendal Broadie

Kendal Broadie, Ph.D. Principal Investigator
Charles Tessier, Ph.D. Postdoctoral Fellow
Vanderbilt University

FRAXA Awards:
$40,000 in 2006
$35,000 in 2000

By Kendal Broadie, 3/2006

Over the past 4 years, we have developed an exciting new genetic model of Fragile X Syndrome in that best-characterized genetic workhorse system; the fruitfly Drosophila melanogaster. We previously generated mutant animals lacking or over-expressing the Drosophila Fragile X protein, dFMRP, and demonstrated that mutant animals manifest the characteristic hallmarks of the disease including both neuronal and behavioral defects. An exciting hypothesis developing over the last few years suggests that FMRP may be regulated downstream of signaling via metabotropic glutamate receptors (mGluRs). The mGluR hypothesis suggests that FMRP functions to limit neuronal activity in response to these receptors. In response to this advancing idea, we generated mutant animals lacking or over-expressing the sole mGluR present in Drosophila (dmGluRA). These efforts now place us in a position to genetically test the mGluR hypothesis of Fragile X Syndrome, which will be the focus of the funded work.

Charles Tessier

Initially, our efforts will be to compare and contrast the characteristics of mutant neurons with altered levels of dmGluRA and dFMRP. These analyses will use various levels of microscopy, electrophysiology and extend to the study of output behavior. The goal will be to determine the degree to which dmGluRA and dFMRP operate in the same neurological pathways. We will then assay any changes to these convergent phenotypes in response to drug treatments that either enhance or inhibit mGluR signaling. A critical aspect of this analysis will be to determine whether drug treatments are ineffective in animals that lack both dmGluR and dFMRP, thus testing the specificity of the drug targets. We will more specifically test the nature of the dmGluRA-dFMRP signaling interaction using a combination of genetic studies and microarray technologies.

Synaptic Plasticity and Olfactory Learning in a mouse model of fragile X syndrome

Kendal Broadie, Ph.D. Principal Investigator
Yong Zhang, Ph.D. Postdoctoral Fellow
University of Utah

By Yong Zhang and Kendal Broadie, 3/2001

One of the most compelling challenges in fragile X research is to understand how lack of the affected protein (FMRP) gives rise to mental impairment and associated

behavioral abnormalities. A potentially fruitful approach is to assay FRAXA gene (FMR1) function within a simple, well-characterized genetic model organism such as the fruitfly, Drosophila melanogaster. Drosophila has a long and distinguished history as a genetic system to assay underlying causes of inherited human genetic diseases. In the last few years, Drosophila has contributed enormously to our understanding of a number of common neurodegenerative diseases including Alzheimer's and Parkinson's disease. We anticipate a similar revolution in our understanding of fragile X through developing a Drosophila model.

Last year, we identified and characterized a Drosophila FMR1 gene homologue (i.e. highly similar gene) which is now named dFMR1. Like its human counterpart, the dFMR1 protein product is highly expressed in most, if not all, nerve cells of the central nervous system, from embryogenesis to adulthood. Like human patients, when dFMR1 is completely removed from the fly genome (i.e. null mutants), the mutant fly is fully viable and morphologically normal, but exhibits uncoordinated movement behaviors. Microscopic assays of these mutants show that neuronal synapses (where a neuron communicates with another neuron or with a muscle cell) develop abnormally, resulting in clear structural defects. When dFMR1 is over-expressed in transgenic flies, making excess protein, an opposite structural change is observed. These results show that the level of dFMR1 protein directly dictates the level of synaptic structural development. Similarly, electrophysiological assays of synaptic function in both mutants and transgenic flies show that neurotransmission is abnormal, in agreement with the severity of the structural defects. These phenotypes, together with complementary human and mouse studies, strongly suggest that fragile X Syndrome may result from synaptic defects.

This year, we will focus on looking for dFMR1 interacting partners by employing powerful genetic interaction screens available only in Drosophila. We will mutate the entire fruit fly genome while screening for genes which can ameliorate fragile X symptoms in flies. Identifying and characterizing genes which interact with dFMR1 will help us understand the mechanism by which the fragile X gene and its protein product perform their normal function - and what goes wrong in the absence of the protein. We intend to use this information to develop treatments for fragile X.

This grant was approved by FRAXA's Directors for a second year of funding, but, happily, it will be funded at a higher level by the NIH/FRAXA joint funding initiative. A small bridge grant was awarded until the NIH funding kicked in.